Alcohol dehydrogenase and *aldehyde dehydrogenase* polymorphisms and colorectal cancer: The Fukuoka Colorectal Cancer Study

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Alcohol dehydrogenase and aldehyde dehydrogenase are key enzymes in alcohol metabolism and therefore may be of importance to colorectal cancer development. The present case–control study was conducted to determine the influence of *ADH2, ADH3* and *ALDH2* polymorphisms in Fukuoka, Japan, with 685 incident cases of histologically confirmed colorectal adenocarcinomas and 778 community controls selected randomly from the study area. Alcohol use was ascertained by in-person interview. Statistical adjustment was made for sex, age class, area, and alcohol use. Individuals with the allele *47Arg* of the *ADH2* polymorphism (slow metabolizers) had a statistically significant increase in risk, with an adjusted OR of 1.32 (95% CI = 1.07–1.63), compared with those having the *ADH2*47His/His* genotype. This association was not affected by the level of alcohol consumption. The *ADH3* polymorphism showed no measurable association with the risk of colorectal cancer on either overall analysis or stratified analysis with alcohol use. The heterozygous *ALDH2*487Glu/Lys* genotype was not associated with an increase in the risk of colorectal cancer (adjusted OR 0.89, 95% CI = 0.71–1.13) compared with the *ALDH2*487Glu/Glu* genotype. Rather unexpectedly, the homozygous *ALDH2*487Lys/Lys* genotype was related to a statistically significantly decreased risk of colorectal cancer (adjusted OR 0.55, 95% CI = 0.33–0.93). It is unlikely that acetaldehyde metabolism determined by *ALDH2* polymorphism contributes to the risk of colorectal cancer, whereas the role of *ADH2* polymorphism deserves further investigation. (*Cancer Sci* 2007; 98: 1248–1253)

Alcohol consumption has fairly consistently been related to an increased risk of colorectal cancer.[1] In a pooled analysis of eight cohort studies in North America and Europe, a consumption of ≥45 g of alcohol per day was associated with a 1.4-fold increase in the risk of colorectal cancer.[2] A positive association between alcohol and colon or colorectal cancer has also been observed in Asian countries,[3–7] with few exceptions.[8] However, uncertainty remains as to the biological mechanisms for the association between alcohol use and colorectal cancer.

Ethanol is first oxidized to acetaldehyde by ADH, and acetaldehyde is further metabolized to acetate by ALDH. Human ADH exhibits several isoenzymes, and functional polymorphisms are known for the *ADH2* and *ADH3* genes.[9] A polymorphism in exon 3 of the *ADH2* gene, resulting in an arginine to histidine substitution in codon 47, affects the enzyme activity substantially. Individuals that are homozygous for the *ADH2*47His* allele (previously called *ADH2*2*) metabolize ethanol 40 times faster than those homozygous for the *ADH2*47Arg* allele (previously called *ADH2*1*).[10] The enzyme activity of *ADH2*47His/Arg* genotype is in the intermediate range between the two homozygous genotypes.[11] The polymorphic site for the *ADH3* gene is *Ile349Val* in exon 8. Maximal velocity is 2.5-fold greater in individuals homozygous for the *ADH3*349Ile* allele (previously called *ADH3*1*) than in those homozygous for the *ADH3*349Val* allele (previously called *ADH3*2*).[10] The *ADH2*47His* allele is fairly common in Asian populations and rare in Caucasians, while the *ADH3*349Val* allele is more frequent in Caucasians than in Asians.[12] *ALDH2* is the gene encoding mitochondrial ALDH, which contributes the majority of acetaldehyde oxidation in human liver and contains a functional polymorphism of *Glu487Lys*, with the variant *ALDH2*487Lys* (previously called *ALDH2*2*) allele resulting in an inactive form. The *ALDH2*487Lys* allele is mainly found in Asian populations.[12,13]

Several studies have investigated the relation of genetic polymorphisms of these alcohol-metabolizing enzymes to colorectal cancer and adenomas. As regards the *ADH2* polymorphism and colorectal cancer, a moderate increase in the risk of colorectal cancer was observed for each of the *Arg*/*His* and *Arg*/*Arg* genotypes compared with the *His*/*His* genotype in Japan,[14] but not in Spain.[15] The *ADH3* polymorphism was unrelated to colorectal cancer in two studies of Caucasians,[16,17] but one of these suggested an effect modification of alcohol consumption.[16] Two studies have examined the relation between *ADH3* polymorphism and colorectal adenomas in Caucasians, producing inconsistent results.[18,19] Although there was no difference in the distribution of *ADH3* genotypes between adenoma cases and controls in these studies, one showed a moderate increase in the risk of adenoma in men and women with the *ADH3*349Ile/Ile* genotype compared with those with the *ADH3*349Ile/Val* or *ADH3*349Val/Val* genotypes when alcohol consumption was high,[18] whereas the other reported an increased risk of adenoma associated with the *ADH3*349Val* allele for men with high alcohol consumption.[19] Studies regarding the *ALDH2* polymorphism and colorectal cancer or adenomas have all been done in Japan.[14,20–23] An approximately 3-fold increase in the risk of colorectal cancer has been observed for *ALDH2*487Glu/Lys* versus *ALDH2*487Glu/Glu* among alcoholics.[20] Another study

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Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio; PCR–RFLP, polymerase chain reaction–restriction fragment length polymorphism.

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suggested a greater increase in the risk of colon cancer, not of rectal cancer, associated with high alcohol consumption among individuals with the *ALDH2*487Glu/Lys* genotype.[21] A small case–control study showed a positive interaction between high alcohol consumption and the *ALDH2*487Glu/Lys* genotype, particularly on the risk of rectal cancer.[22] In contrast, the *ALDH2* polymorphism did not show any measurable association with either colorectal cancer or adenomas in recent studies.[14,23]

The present paper examines the relation of the *ADH2*, *ADH3* and *ALDH2* polymorphisms to colorectal cancer in a case–control study in Japan, focusing on effect modification of alcohol consumption and gene–gene interaction.

Materials and Methods

The Fukuoka Colorectal Cancer Study is a case–control study of incident cases and community controls, with Fukuoka City and three adjacent areas as the catchment area. Details have been reported previously.[24] Described below are methods relevant to the present analysis. The study protocol was approved by the ethical committees of Kyushu University and of all but two of the participating hospitals. There was no ethical committee at the two hospitals, and the survey was done at these hospitals with permission from the director of each hospital.

Subjects. Cases comprised a consecutive series of patients with histologically confirmed incident colorectal adenocarcinomas who were admitted to two university hospitals or six affiliated hospitals for surgical treatment during the period from October 2000 to December 2003. Other eligibility criteria included the following characteristics: age of 20–74 years at the time of diagnosis, residence in the study area, no prior history of partial or total removal of the colorectum, familial adenomatous polyposis or inflammatory bowel disease. Of the total of 1053 eligible cases, 840 cases (80%) participated in the interview, and 685 (65%) gave informed consent to genotyping.

Eligibility criteria for controls were the same as described for cases except for two items, that is, having no diagnosis of colorectal cancer and age of 20–74 years at the time of selection. A total of 1500 persons were selected as control candidates using two-stage random sampling from among residents living in 15 small areas. A total of 833 persons participated in the survey, and 778 gave informed consent to genotyping. Reasons for exclusion and non-participation were death ($n = 7$), migration from the study area ($n = 22$), undelivered mail ($n = 44$), mental incompetence ($n = 19$), history of partial or total removal of the colorectum ($n = 21$), diagnosis of colorectal cancer after the survey ($n = 5$), no response ($n = 158$), and refusal ($n = 391$). After exclusion of the first six categories of outcomes ($n = 118$), net participation rates were calculated as 60% (833/1382) for the interview and 56% (778/1382) for genotyping.

Interview. Research nurses interviewed cases and controls in person regarding physical activity, smoking, alcohol use, and other factors using a uniform questionnaire. Habitual alcohol consumption at the time 5 years prior to the onset of disease in cases or the interview in controls was ascertained. Individuals reported the average number of days per week that alcohol was consumed and the average amount of alcohol per day of drinking. The amount of alcohol was expressed by the conventional unit; one *go* (180 mL) of *sake*, one large bottle (633 mL) of beer, and half a *go* (90 mL) of *shochu* were each expressed as one unit; and one drink (30 mL) of whisky or brandy and one glass (100 mL) of wine were each converted to half a unit. The reproducibility of the questionnaire was tested on 29 control subjects (14 men and 15 women) with an interval of approximately 1 year, and the reported alcohol intake was highly reproducible (Spearman's $r = 0.82$).

Genotyping. A venous blood sample of 5 mL was taken after the interview. DNA was extracted from the buffy coat using a commercial kit (QIAGEN GmbH, Hilden, Germany) and genotyping was performed using the PCR–RFLP method. The PCR was performed in a reaction mixture of 10 μL containing 0.5 IU of Taq and 1 μL of template DNA with a concentration of approximately 50–150 ng/μL. The *ADH2 Arg47His* and *ADH3 Ile349Val* genotypes were determined according to the methods described by Osier *et al*.[25] Primers for the *ADH2 Arg47His* genotypes were 5′-ATT CTA AAT TGT TTA ATT CAA GAA g-3′ (sense) and 5′-ACT AAC ACA GAA TTA CTG GAC-3′ (antisense). PCR products were digested with 20 IU of *Msl*I for 16 h at 37°C in a mixture of 20 μL, resulting in fragments of 443 bp and 242 bp for the *47His* allele and 685 bp for the *47Arg* allele. The *ADH3 Ile349Val* genotypes were determined using primers of 5′-TTG TTT ATC TGT GAT TTT TTT TGT-3′ (sense) and 5′-CGT TAC TGT AGA ATA CAA AGC-3′ (antisense). The PCR product of 378 bp fragments was digested with 5 IU of *Ssp*I in a reaction mixture of 20 μL for 3 h at 37°C, resulting in fragments of 274 bp and 104 bp for the *349Ile* allele and 378 bp for the *349Val* allele. The *ALDH2 Glu487Lys* genotypes were determined, as described by Goedde *et al*.,[26] using primers that were 5′-CAA ATT ACA GGG TCA ACT GCT-3′ (sense) and 5′-CCA CAC TCA CAG TTT TCT CTT-3′ (antisense). The PCR product was digested with *Ksp632I* (10 IU) or *EarI* (10 IU) for 12 h at 37°C in a mixture of 20 μL, resulting in fragments of 112 bp for the *ALDH2*487Glu* allele and 135 bp for the *ALDH2*487Lys* allele. The digested PCR products were separated using electrophoresis on 3% agarose gels (NuiSieve GTG, Rockland, ME, USA), and visualized with ethidium bromide.

Statistical analysis. The association of the genetic polymorphisms with risk of colorectal cancer was examined using multiple logistic regression analysis including indicator variables for sex, 5-year age class (the lowest class was <40 years), resident area (Fukuoka City or adjacent areas), and alcohol intake (0, 0.1–1.9, or ≥2.0 units per day) as covariates. Adjusted OR and 95% CI were obtained from the logistic regression coefficient and the standard error for the corresponding indicator variable. Statistical significance for the interaction was tested using the likelihood ratio test comparing the logistic models with and without interaction terms for the genotype and alcohol category. Statistical significance was concluded if the two-sided *P*-value was less than 0.05 or if the 95% CI did not include unity. All statistical analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA).

Results

The number of men among the 685 cases and 778 controls was 426 (62%) and 490 (63%), respectively. The mean age of the cases was 60 years (range 27–74), and that of the controls was 59 years (range 22–75). More than half of the cases (61%) and controls (64%) were residents of Fukuoka City. All of the distributions of genotypes for the *ADH2 Arg47His*, *ADH3 Ile349Val*, and *ALDH2 Glu487Lys* polymorphisms were in agreement with the Hardy–Weinberg equilibrium in both cases and controls. The alcohol-drinking pattern differed strikingly by *ALDH2* polymorphism and slightly so with respect to the *ADH2* polymorphism (Fig. 1). Alcohol use was progressively less frequent with increasing numbers of the *ALDH2*487Lys* allele, and was slightly more frequent with increasing numbers of the *ADH2*47Arg* allele. There was no variation in the proportion of alcohol drinking according to the *ADH3 Ile349Val* polymorphism (data not shown).

Regarding the *ADH2* polymorphism, the *47Arg* allele was slightly more frequent in cases than in controls, and the adjusted OR for the *Arg/His* and *Arg/Arg* genotypes as compared with the *His/His* genotype were each greater than unity, the increase for the heterozygote being statistically significant (Table 1). The adjusted OR for those with the *ADH2*47Arg* allele compared

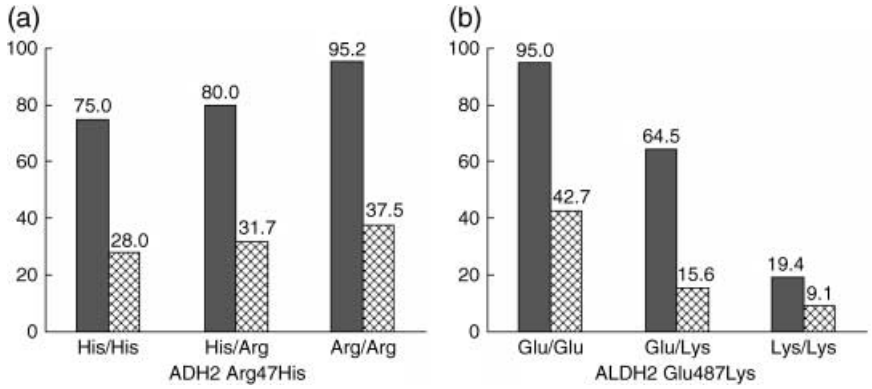

Fig. 1. Proportions (%) of alcohol drinkers for men (gray bar) and women (hatched bar) according to the *ADH2 Arg47His* and *ALDH2 Glu487Lys* polymorphisms in the control group. Values shown at the top of each bar are percentages of alcohol drinkers. Trend *P*-values were 0.03 in men and 0.35 in women for the *ADH2* polymorphism, and <0.0001 in both sexes for the *ALDH2* polymorphism. The trend *P*-value was based to the Mantel-Haenszel method with scores of 0, 1, and 2 assigned for the number of the variant allele.

Table 1. Relation of *ADH2*, *ADH3*, and *ALDH2* polymorphisms to colorectal cancer risk

Genotype	Cases (*n*, %)	Controls (*n*, %)	Adjusted OR (95% CI)†
ADH2 Arg47His‡			
His/His (fast)	345 (50.8)	452 (58.1)	1.00 (referent)
Arg/His	294 (43.3)	289 (37.1)	1.32 (1.06–1.64)
Arg/Arg (slow)	40 (5.9)	37 (4.8)	1.36 (0.84–2.20)
ADH3 Ile349Val§			
Ile/Ile (fast)	609 (88.9)	706 (90.9)	1.00 (referent)
Ile/Val	74 (10.8)	68 (8.7)	1.29 (0.91–1.83)
Val/Val (slow)	2 (0.3)	3 (0.4)	0.77 (0.13–4.70)
ALDH2 Glu487Lys			
Glu/Glu	400 (58.4)	416 (53.5)	1.00 (referent)
Glu/Lys	257 (37.5)	309 (39.7)	0.89 (0.71–1.13)
Lys/Lys (null activity)	28 (4.1)	53 (6.8)	0.55 (0.33–0.93)

†Adjusted for sex, 5-year age class, area, and alcohol use. ‡Six cases were excluded because of undetermined genotype. §One control was excluded because of undetermined genotype. CI, confidence interval; OR, odds ratio.

with those without was 1.32 (95% CI = 1.07–1.63). There was no measurable difference in the distribution of *ADH3 Ile349Val* genotypes between cases and controls. The *ALDH2***487Lys* allele was less frequent in cases than in controls, and the adjusted OR of colorectal cancer for the *Lys*/*Lys versus Glu*/*Glu* genotype was statistically significantly lower than unity. Analysis by sex showed similar results for men and women. For instance, the adjusted OR for *ADH2***47Arg*/*His* and *Arg*/*Arg* genotypes combined were 1.34 (95% CI = 1.03–1.75) in men and 1.35 (95% CI = 0.95–1.91) in women. Regarding the *ALDH2* polymorphism, the adjusted OR for the *Glu*/*Lys* and *Lys*/*Lys* genotypes compared with the *Glu*/*Glu* genotype in men were 0.77 (95% CI = 0.56–1.05) and 0.44 (95% CI = 0.22–0.91), respectively, while the corresponding values in women were 1.04 (95% CI = 0.71–1.53) and 0.67 (95% CI = 0.31–1.46), respectively.

Table 2 summarizes the results from the analysis regarding the interaction between alcohol intake and each genetic polymorphism. In this analysis, individuals heterozygous for the *ADH2* or *ADH3* polymorphism were each combined with those homozygous for the variant allele. Individuals homozygous for the variant allele of *ALDH2* (*487Lys*/*Lys*) were excluded because alcohol use was almost null in this group. There was no appreciable effect modification of each polymorphism on the relation between alcohol and colorectal cancer. High alcohol consumption was related to a moderate increase in the OR of colorectal cancer regardless of the genotype. Adjusted OR for high alcohol use (≥2 units/day) versus no use after control for the *ADH2*, *ADH3*, and *ALDH2* genotypes each were 1.34 (95% CI = 0.99–1.82), 1.37 (95% CI = 1.01–1.85) and 1.20 (95% CI = 0.85–1.69), respectively.

The joint effects of the *ADH2* or *ADH3* polymorphism in combination with the *ALDH2* polymorphism were examined among alcohol drinkers (Table 3). Individuals with the *ADH2***47His*/*His* genotype and the *ALDH2***487Lys* allele showed a statistically non-significant, small decrease in the OR for colorectal cancer. No such decrease was noted on analysis of the non-alcohol drinkers (data not shown). There was no clear interaction between the *ADH3* and *ALDH2* polymorphisms on the risk of colorectal cancer in either non-alcohol drinkers or alcohol drinkers.

Discussion

The present study addressed the relation between genetic polymorphisms in alcohol metabolism and colorectal cancer. Individuals with the *ADH2***47Arg* allele (slow metabolizers) showed a modest, but statistically significant, increase in the risk of colorectal cancer. In contrast, individuals homozygous for the *ALDH2* variant allele had a decreased risk of colorectal cancer. None of the polymorphisms affected the relation between alcohol and colorectal cancer. Because of the limited variation in the *ADH3* polymorphism, the present study did not provide useful information regarding the role of *ADH3* polymorphism in colorectal carcinogenesis.

Both *ADH2* and *ADH3* polymorphisms have been shown to affect the risk of various alcohol-related conditions. The slow alcohol metabolism of *ADH3* polymorphism has been related to increased risk of alcoholism and liver cirrhosis, elevated levels of serum HDL cholesterol, and decreased risk of myocardial infarction in Western populations.[27,28] Studies in Japan have reported that the slow metabolizers with the *ADH2* polymorphism had an increased risk of alcoholic liver disease,[29] and of cerebral infarction.[30] However, it remains uncertain whether these polymorphisms affect the risk of alcohol-related cancers. In a meta-analysis of seven case–control studies, no association between *ADH3*

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Table 2. Combined effects of *ADH2*, *ADH3*, and *ALDH2* polymorphisms with alcohol use on the risk of colorectal cancer

Genotype		Alcohol intake (unit/day)†		
		0	<2	≥2
ADH2 Arg47His				
His/His	No.‡	142/192	109/167	94/93
	OR (95% CI)§	1.00 (referent)	0.97 (0.69–1.37)	1.52 (1.02–2.25)
Arg/His + Arg/Arg	No.	128/119	109/123	97/84
	OR (95% CI)	1.46 (1.04–2.03)	1.30 (0.92–1.85)	1.69 (1.14–2.52)
		Interaction $P = 0.61$		
ADH3 Ile349Val				
Ile/Ile	No.	235/281	199/266	175/159
	OR (95% CI)	1.00 (referent)	0.98 (0.74–1.28)	1.44 (1.05–1.98)
Ile/Val + Val/Val	No.	37/30	22/23	17/18
	OR (95% CI)	1.49 (0.89–2.50)	1.29 (0.70–2.40)	1.27 (0.62–2.57)
		Interaction $P = 0.49$		
ALDH2 Glu487Lys¶				
Glu/Glu	No.	98/103	150/171	152/142
	OR (95% CI)	1.00 (referent)	1.04 (0.71–1.53)	1.24 (0.81–1.90)
Glu/Lys	No.	147/163	71/112	39/34
	OR (95% CI)	1.02 (0.71–1.48)	0.74 (0.47–1.17)	1.33 (0.74–2.39)
		Interaction $P = 0.30$		

†One unit of alcohol intake corresponded to 1 go (180 mL) of *sake*, 0.5 go (90 mL) of *shochu*, 1 large bottle (633 mL) of beer, 2 drinks (60 mL) of whiskey, or 2 glasses (200 mL) of wine. ‡Numbers of cases/controls. §Adjusted for sex, 5-year age class, and area. ¶Individuals with 487Lys/Lys genotype were excluded, because alcohol drinkers were few. CI, confidence interval; OR, odds ratio.

Table 3. Combined effects of *ADH2* or *ADH3* polymorphism with the *ALDH2* polymorphism on the risk of colorectal cancer in alcohol drinkers

ADH2/ADH3		*ALDH2 Glu487Lys*	
		Glu/Glu	*Glu/Lys*
ADH2 Arg47His			
His/His	No.†	153/170	50/84
	OR (95% CI)‡	1.00 (referent)	0.70 (0.46–1.07)
Arg/His + Arg/Arg	No.	148/143	57/62
	OR (95% CI)	1.12 (0.81–1.55)	1.08 (0.70–1.67)
		Interaction $P = 0.30$	
ADH3 Ile349Val			
Ile/Ile	No.	274/283	100/135
	OR (95% CI)	1.00 (referent)	0.83 (0.60–1.14)
Ile/Val + Val/Val	No.	28/30	10/11
	OR (95% CI)	1.00 (0.58–1.74)	0.98 (0.40–2.38)
		Interaction $P = 0.76$	

†Numbers of cases/controls. ‡Adjusted for sex, 5-year age class, area, and alcohol use low or high intake. CI, confidence interval; OR, odds ratio.

polymorphism and upper aerodigestive cancers was found, nor was any interaction between *ADH3* polymorphism and alcohol consumption on the risk of these cancers.[12] A study of Japanese alcoholics has showed increased risks of oral, laryngeal, and esophageal cancer for the *ADH2*47Arg/Arg* genotype,[31] while another study in Japan showed no effect modification of the *ADH2* polymorphism on the association between alcohol and esophageal cancer.[32]

A recent Japanese study reported a positive association between the *ADH2* polymorphism and colorectal cancer, showing a progressive increase in the risk with increasing numbers of the *ADH2*47Arg* allele.[14] No such progressive increase in the risk was observed in the present study, but the authors' findings are compatible with the previous observation in that the risk was elevated in individuals with the *ADH2*47Arg* allele. The authors have no clear explanation for the increased risk of colorectal cancer associated with the *ADH2* polymorphism, but the consistency in the two independent studies warrants further investigation regarding the role of the *ADH2* polymorphism in colorectal carcinogenesis.

The present study showed neither an increased risk of colorectal cancer associated with the *ALDH2*487Lys* allele nor interaction between the *ALDH2*487Lys* allele and alcohol consumption. These findings are at odds with results from previous studies of colorectal cancer,[20–22] but are consistent with the recent observations on colorectal cancer,[14] and adenomas.[23] The statistically significant decrease in the risk of colorectal cancer associated with the *ALDH2*487Lys/Lys* genotype was rather unexpected and difficult to interpret. A decrease in the OR associated with the *Lys/Lys* genotype was also observed in the analysis confined to non-drinkers of alcohol ($n = 583$), although the decrease was not statistically significant; adjusted OR for the *Glu/Glu*, *Glu/Lys*, and *Lys/Lys* genotypes were 1.00 (referent), 1.00 (95% CI = 0.68–1.46), and 0.64 (95% CI = 0.36–1.14), respectively. The decreased risk in individuals with the *ALDH2487Lys/Lys* genotype may have been due to residual confounding of lifestyle factors other than alcohol drinking. In the Fukuoka Colorectal Cancer Study, obesity and physical inactivity were related to increased risk,[33] and there was a protective association with intake of n-3 polyunsaturated fatty acids.[34] With further

adjustment for these factors as well as for dietary calcium and fiber using the variables and categories as defined previously,[34] the adjusted OR for the *Glu*/*Lys* and *Lys*/*Lys* genotypes versus the *Glu*/*Glu* genotype were 0.90 (95% CI = 0.70–1.14) and 0.52 (95% CI = 0.31–0.88), respectively, in the analysis excluding four cases and two controls with a total calorie intake estimated to be >20 929 kJ/day. While a similar, inverse association was noted for colorectal adenomas,[23] no such association was seen in another study of colorectal cancer in Japan.[14]

It is hypothesized that acetaldehyde is accumulated in individuals who are fast alcohol metabolizers and slow acetaldehyde metabolizers.[29] Thus the authors hypothesized that the combination of *ADH2*His*/*His* and *ALDH2*487Glu*/*Lys* genotype might be related to an increased risk of colorectal cancer, but the risk of colorectal cancer was decreased, rather than increased in alcohol drinkers with such composite genotypes.

This finding on the gene–gene interaction, together with the above-mentioned findings on the *ALDH2* polymorphism, suggests that acetaldehyde metabolism in the liver is not measurably linked to colorectal carcinogenesis. Bacterial production of acetaldehyde in the colon is an alternative mechanism by which alcohol may enhance colorectal carcinogenesis. Human colonic contents and isolated colonic microbes are capable of producing acetaldehyde when incubated with ethanol *in vitro*.[35,36] It has been demonstrated in piglets that high levels of acetaldehyde were produced in the colon during normal metabolism of alcohol.[37] ALDH activity is much lower in the colonic mucosa than in the liver,[38,39] and colonic epithelial cells are exposed to high concentrations of acetaldehyde in the colonic lumen. It is hypothesized that low folate status increases the risk of colorectal cancer by altering DNA methylation and DNA synthesis.[40,41] Alcohol and acetaldehyde exert adverse effects on folate metabolism.[42] High alcohol consumption results in inadequate folate status by decreasing intestinal absorption and increasing renal excretion. It is known that acetaldehyde rather than alcohol itself cleaves folate chemically. Ethanol ingestion has resulted in a substantial increase in the intracolonic concentration of acetaldehyde and decreased folate levels in the colonic mucosa in an experimental study of rats.[43]

The present study is probably the largest that has ever been reported regarding the *ADH2* or *ALDH2* polymorphism and colorectal cancer. Among the reported studies are those including 257 colorectal cancer cases and 771 controls,[14] 270 cases and 121 controls,[21] and 142 cases and 241 non-cancer controls,[22] in Japan. The size of a study is particularly important in investigating the role of rare genotypes in the gene–environment or gene–gene interaction. The participation rate in terms of genotyping was not so high in either cases (65%) or controls (56%). Because the *ADH2* and *ALDH2* polymorphisms affected alcohol drinking, a selection bias would be possible in the association with these polymorphisms if cases and controls participated in the study differentially with respect to alcohol drinking. Among those interviewed, however, the proportions of alcohol drinking in the cases and controls each did not differ by consent to genotyping.[44] Alcohol consumption 5 years prior to the referent date was used, and the authors have no data as to how valid the recalled alcohol consumption in the past was, although it was found to be highly reproducible.

In summary, a case–control study in Japan showed an increased risk of colorectal cancer associated with the *ADH2*47Arg* allele, but not with the *487Lys* allele of *ALDH2* polymorphism. None of the polymorphisms affected the relation between alcohol consumption and colorectal cancer risk. It is unlikely that acetaldehyde metabolism determined by *ALDH2* polymorphism contributes to the risk of colorectal cancer, whereas the role of *ADH2* polymorphism deserves further investigation.

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